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Intravascular Ultrasound Assessment of Patterns of Arterial Remodeling in the Absence of Significant Reference Segment Plaque Burden in Patients With Coronary Artery Disease

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OBJECTIVES We evaluated the impact of reference vessel segment plaque burden on lesion remodeling.

BACKGROUND Intravascular ultrasound (IVUS) assessment of lesion remodeling compares lesions to reference segments. However, reference segments are rarely disease-free and, therefore, have also undergone remodeling changes.

METHODS Pre-intervention IVUS was obtained in 274 patients with right coronary artery lesions selected because the right coronary artery has less tapering and fewer side branches than the left anterior descending or left circumflex artery. Standard IVUS definitions were used. Patients were divided according to reference vessel segment plaque burden: group A (minimal reference disease, n = 91), both proximal and distal reference plaque burden <20%; group B (n = 91), either proximal or distal reference plaque burden 20% to 40% but both ≤40%; and group C (n = 92), either proximal or distal reference plaque burden >40%.

RESULTS The remodeling index measured 0.98 ± 0.16 in group A (range, 0.68 to 1.47), 1.04 ± 0.18 in group B (range, 0.67 to 1.91), and 1.04 ± 0.15 in group C (range, 0.74 to 1.70), analysis of variance p = 0.0208 (p = 0.0234 group A vs. group B and p = 0.0012 group A vs. group C, but p = 0.8 group B vs. group C). Positive, intermediate, and negative remodeling were observed in 24 (26%), 24 (26%), and 43 lesions (48%) in group A; 36 (40%), 28 (30%), and 27 lesions (30%) in group B; and 34 (37%), 39 (42%), and 19 lesions (21%) in group C, respectively (p = 0.0022).

CONCLUSIONS Negative remodeling occurs commonly in coronary lesions with minimal reference segment disease. Negative remodeling is not just an "artifact" introduced by comparing lesions to diseased reference segments. (J Am Coll Cardiol 2003;42:806–10) © 2003 by the American College of Cardiology Foundation

Arterial remodeling is commonly observed in human atherosclerosis. It is a heterogeneous response ranging from positive remodeling (increase in arterial dimensions, especially in reference segments and in lesions responsible for acute coronary syndromes) to negative remodeling (decrease in arterial dimensions, especially in hemodynamically significant stenoses in patients with chronic stable angina) (1–4). In vivo assessment of lesion site remodeling using intravascular ultrasound (IVUS) is usually performed by comparing the lesion to the reference segments (5). However, the reference segments are rarely disease-free and, therefore, have also undergone remodeling changes (6). The purpose of the current study is to report the assessment of remodeling in patients with minimal reference segment disease in order to reduce the impact of reference segment remodeling on lesion site assessment.

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METHODS

Study population. From February 1999 to April 2002, 3,940 native artery lesions were treated at Asan Medical Center. Intravascular ultrasound imaging was performed in 2,680 lesions (68%). Use of IVUS before coronary intervention was at the operator's discretion and was performed in 1,347 (50%) of 2,680 lesions: 746 left anterior descending; 134 left circumflex; 82 left main; and 385 right coronary. Because the right coronary artery has less vessel tapering and fewer side branches compared with left anterior descending or left circumflex arteries (7), the right coronary artery was selected for analysis. We excluded severely calcific lesions (n = 32), long lesions (lengths >20 mm, n = 64), restenotic lesions (n = 3), and inability to evaluate the proximal or

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Abbreviations and Acronyms
CSA = cross-sectional area
EEM = external elastic membrane
IVUS = intravascular ultrasound
P&M = plaque and media

distal reference segment due to ostial location or large side branches (n = 12). Therefore, pre-intervention IVUS images of de novo right coronary lesions were obtained in 274 patients. All patients had objective evidence of myocardial ischemia and ≥50% angiographic diameter stenosis visual estimate.

IVUS imaging protocol. Pre-intervention IVUS was performed after intracoronary administration of 0.2 mg nitroglycerin using motorized transducer pullback system (0.5 mm/s) and commercial scanner (SCIMED, Boston Scientific Scimed Inc., Minnesota) consisting of a 30 MHz transducer within 3.2F imaging sheath. Ultrasound studies were recorded on 1/2-in high-resolution s-VHS tape for off-line analysis.

Quantitative IVUS measurements. Validation of cross-sectional area (CSA) measurements of external elastic membrane (EEM), lumen, and plaque and media (P&M) by IVUS have been reported (8). The pre-intervention lesion site was the image slice with the smallest lumen CSA. The proximal and distal reference segments were the most normal-looking segments (largest lumen with smallest plaque burden) within 5 mm proximal and distal to the lesion. The target lesion and both proximal and distal reference segments were assessed quantitatively. At each image slice, EEM, lumen, and P&M (= EEM − lumen) CSA were measured with a commercially available program for computerized planimetry (TapeMeasure, Indec System, California). The plaque burden was measured as 100 × (P&M CSA/EEM CSA).

The remodeling index was defined as lesion EEM CSA divided by mean reference EEM CSA (the average of the proximal and distal reference segments). Our previous study in patients with variant angina and early atherosclerosis showed that the reference segment plaque burden was mostly 20% to 40% (9). Therefore, the patients were divided into three equal groups (terciles) according to reference segment disease: 1) group A (minimal disease), both proximal and distal reference plaque burden <20%, 2) group B, either proximal or distal reference plaque burden between 20% and 40% but both <40%, and 3) group C (significant disease), either proximal or distal reference plaque burden >40%. Positive remodeling was defined as a remodeling index >1.05, negative remodeling as a remodeling index <0.95, and intermediate remodeling as a remodeling index between 0.95 and 1.05 (4).

Calcium was measured in degrees with an electronic protractor centered on the lumen. Plaque was classified visually as hypoechoic or fibrotic (hyperechoic) (5).

To assess reproducibility, two independent observers measured EEM and lumen CSA. Intra- and inter-observer variabilities (beginning with frame selection) were calculated on 60 randomly selected reference segments (Table 1).

Table 1. Intra- and Inter-Observer Variability of Reference Segment

	Reading 1	Reading 2	Δ	r
Intraobserver variability				
EEM CSA (mm^2)	13.3 ± 4.8	13.3 ± 4.8	0.3 ± 0.2	0.997
Lumen CSA (mm^2)	9.4 ± 3.2	9.5 ± 3.3	0.3 ± 0.2	0.994
Interobserver variability				
EEM CSA (mm^2)	13.3 ± 4.8	13.4 ± 4.8	0.2 ± 0.2	0.999
Lumen CSA (mm^2)	9.4 ± 3.2	9.6 ± 3.4	0.3 ± 0.3	0.996

CSA = cross-sectional area; EEM = external elastic membrane.

Quantitative coronary angiographic analysis. Using the guiding catheter for magnification-calibration and an on-line system (ANCOR V2.0, Siemens, Germany), minimal luminal diameter of lesion segment and reference segment diameter were measured before intervention.

Statistical analysis. Statistical analysis was performed with SPSS software. Data are presented as frequencies or mean ± 1 SD. Comparison was performed with chi-square statistics and analysis of variance (ANOVA). Linear regression analysis was performed to evaluate the correlation between remodeling index versus lesion and reference segment plaque burden. A p value <0.05 was considered statistically significant.

RESULTS

Ninety-one lesions (33%) were in group A, 91 lesions (33%) were in group B, and 92 lesions (34%) were in group C. The overall mean reference segment plaque burden was 28 ± 12% (26 ± 12% and 29 ± 13% for the proximal and distal reference segments, respectively). Among the individual groups, mean reference segment plaque burden was 14 ± 2% in group A (14 ± 3% and 14 ± 2% for proximal and distal reference segments), 28 ± 7% in group B (27 ± 8% and 30 ± 7% for proximal and distal reference segments), and 40 ± 6% in group C (38 ± 10% and 42 ± 6% for proximal and distal reference segments, p < 0.0001 for all inter-group comparisons).

The baseline clinical characteristics are presented in Table 2. There were no significant differences among the three groups.

Intravascular ultrasound findings are shown in Table 3. Reference segment EEM CSA correlated moderately with the reference segment P&M CSA (r = 0.423, p < 0.0001). The remodeling index correlated poorly with the reference segment plaque burden (r = 0.197, p = 0.0010, Fig. 1) and somewhat better with the lesion site plaque burden (r = 0.356, p < 0.0001).

The remodeling index measured 0.98 ± 0.16 in group A (range, 0.68 to 1.47), 1.04 ± 0.18 in group B (range, 0.67 to 1.91), and 1.04 ± 0.15 in group C (range, 0.74 to 1.70): ANOVA p = 0.0208 (p = 0.0234 group A vs. group B and p = 0.0012 group A vs. group C, but p = 0.8 group B vs. group C). Positive, intermediate, and negative remodeling

Table 2. Baseline Clinical Characteristics and Quantitative Coronary Angiographic Data

Group	A	B	C	p Value
Number of patients	91	91	92	
Age (yrs)	58 ± 9	56 ± 11	59 ± 8	0.2
Males, # (%)	70 (77)	73 (80)	76 (83)	0.5
Hypertension, # (%)	34 (37)	35 (38)	40 (43)	0.7
Diabetes mellitus, # (%)	13 (14)	15 (17)	19 (21)	0.5
Lipid profile				
Total cholesterol (mg/dl)	187 ± 43	198 ± 41	196 ± 43	0.2
Triglyceride (mg/dl)	169 ± 122	193 ± 119	159 ± 90	0.2
HDL cholesterol (mg/dl)	41 ± 10	43 ± 27	41 ± 10	0.9
Cigarette smoking, # (%)	38 (42)	39 (43)	34 (37)	0.7
Clinical presentation, # (%)				1.0
Stable angina	21 (23)	26 (29)	23 (25)	
Unstable angina	44 (48)	41 (45)	43 (47)	
Acute myocardial infarction	26 (29)	24 (26)	26 (28)	
Number of diseased vessels, # (%)				0.6
One	47 (52)	43 (47)	51 (55)	
Two	29 (32)	31 (34)	22 (24)	
Three	15 (16)	17 (19)	19 (21)	
Minimal lumen diameter (mm) of lesion segment	0.9 ± 0.7	0.8 ± 0.5	0.9 ± 0.5	0.2
Reference segment diameter (mm)	3.7 ± 0.5	3.6 ± 0.5	3.5 ± 0.5	0.01
Diameter stenosis (%)	76 ± 18	76 ± 14	75 ± 14	0.3

HDL = high-density lipoprotein.

were observed, respectively, in 24 (26%), 24 (26%), and 43 lesions (48%) in group A; 36 (40%), 28 (30%), and 27 lesions (30%) in group B; and 34 (37%), 39 (42%), and 19 lesions (21%) in group C ($p = 0.0022$, Fig. 2).

A multivariate logistic regression analysis was performed for the remodeling pattern as the dependent variable (positive/intermediate/negative) versus the following independent variables: amount of reference segments disease (groups A/B/C); proximal and distal reference lumen dimensions; and plaque characteristic. Only the amount of reference segment plaque burden in group C predicted a reduced frequency of negative remodeling.

With increasing reference plaque burden, the arc of lesion calcium increased, and the frequency of dominant fibrotic lesion plaque characteristics also increased.

DISCUSSION

The current study showed that negative lesion site remodeling occurs in almost half of lesions with minimal reference segment disease (plaque burden in both proximal and distal reference segments <20%). Therefore, negative remodeling is not just an "artifact" introduced by comparing lesions to positively remodeled, diseased reference segments, but oc-

Table 3. IVUS Findings

Group	A	B	C	p Value
Number of patients	91	91	92	
Proximal reference segment				
EEM CSA (mm^2)	17.5 ± 4.7	17.8 ± 4.9	16.7 ± 3.9	0.2
Lumen CSA (mm^2)	15.1 ± 4.3	12.9 ± 3.4	10.4 ± 3.2	< 0.0001
P&M CSA (mm^2)	2.4 ± 0.6	4.9 ± 2.2	6.3 ± 2.2	< 0.0001
Plaque burden (%)	14 ± 3	27 ± 8	38 ± 10	< 0.0001
Lesion				
EEM CSA (mm^2)	16.4 ± 4.8	17.3 ± 5.3	16.4 ± 3.8	0.3
Lumen CSA (mm^2)	2.0 ± 0.3	2.0 ± 0.4	1.9 ± 0.3	1.0
P&M CSA (mm^2)	14.5 ± 4.6	15.4 ± 5.2	14.4 ± 3.7	0.3
Plaque burden (%)	87 ± 3	88 ± 4	88 ± 4	0.6
Arc of calcium (°)	35 ± 73	51 ± 76	70 ± 85	0.0098
Plaque composition, # (%)				< 0.0001
Hypoechoic	64 (70)	44 (48)	29 (32)	
Fibrotic	27 (30)	47 (52)	63 (68)	
Distal reference segment				
EEM CSA (mm^2)	16.2 ± 4.8	15.7 ± 4.6	14.9 ± 3.9	0.1
Lumen CSA (mm^2)	14.0 ± 4.4	10.9 ± 3.3	8.7 ± 2.5	< 0.0001
P&M CSA (mm^2)	2.3 ± 0.5	4.7 ± 1.8	6.2 ± 1.9	< 0.0001
Plaque burden (%)	14 ± 2	30 ± 7	42 ± 6	< 0.0001
Remodeling index	0.98 ± 0.16	1.04 ± 0.18	1.04 ± 0.15	0.0208

CSA = cross-sectional area; EEM = external elastic membrane; IVUS = intravascular ultrasound; P&M = plaque and media.

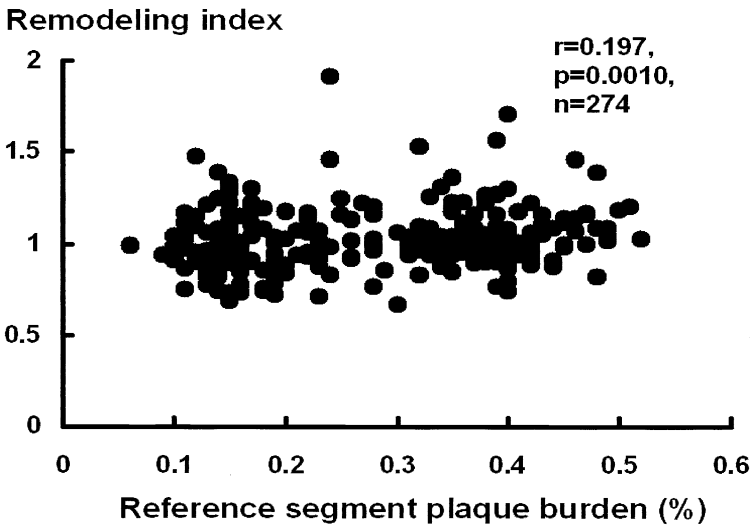

Figure 1. The remodeling index correlated poorly with the reference segment plaque burden ($r = 0.197$, $p = 0.0010$). The remodeling index (and, therefore, the percentage of lesions with positive vs. negative remodeling) does not increase or decrease substantially with increasing reference segment plaque burden.

curs in the absence of even mild reference segment disease. If the absence of mild reference segment disease is taken as a marker of "young" lesion age, this suggests that negative remodeling can occur early during lesion formation.

Previous IVUS studies evaluating coronary arterial remodeling of de novo lesions included all three coronary arteries (1,2). However, vessel (EEM) tapering is greater in left anterior descending and left circumflex arteries than the right coronary artery (7), and left anterior descending and left circumflex lesions are more frequently located near major side branches. External elastic membrane tapering and major side branches may influence the evaluation of arterial remodeling. Therefore, the current study studied only right coronary artery lesions.

Several studies have found that systemic factors (or patient characteristics) influence remodeling patterns. Positive remodeling is more common in hypercholesterolemia (10) and in acute coronary syndromes versus stable angina (4), and negative remodeling is more common in smokers versus nonsmokers (11) and in insulin-using diabetics versus non-insulin-using diabetics (12). Additionally, regional factors such as ostial location and lesion eccentricity also influence remodeling (2). However, these factors do not explain the marked variability in remodeling patterns among lesions in the same artery (2,13). In the current study, these regional factors were not different among the three groups.

To date, true serial IVUS studies of changes in arterial dimensions are rare with the exception of transplant atherosclerosis and restenosis. Therefore, in the assessment of remodeling, lesions must be compared with reference segments. As originally shown by Glagov and confirmed by others (3,14), reference segments undergo positive remod-

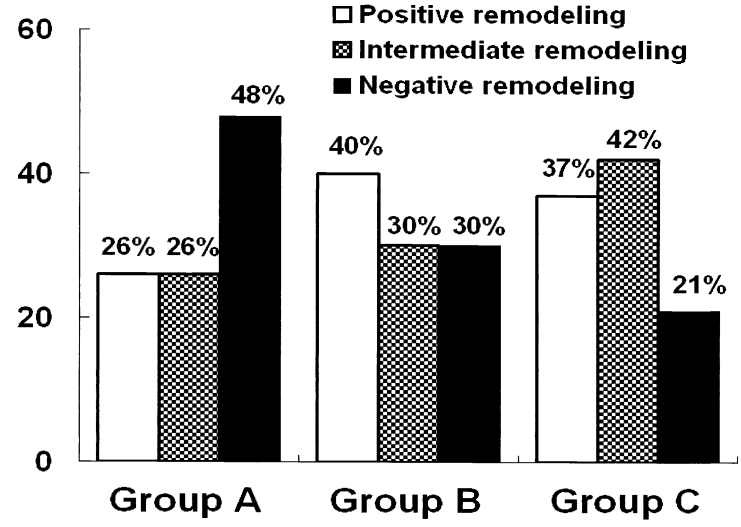

Figure 2. The pattern of arterial remodeling according to reference segment plaque burden is shown ($p = 0.0022$ comparing group A vs. group B vs. group C). Group A, both proximal and distal reference plaque burden <20%; group B, either proximal or distal reference plaque burden between 20% and 40% but both <40%; and group C, either proximal or distal reference plaque burden >40%.

eling to prevent lumen compromise during the development of atherosclerosis. This explains the typical finding of >50% plaque burden in angiographically normal reference segments (14). One difference between reference segments and lesion sites may be the degree to which positive remodeling occurs as well as the amount of plaque burden. Lesions and reference segments with the same plaque mass may be differentiated by the amount of positive versus negative remodeling. Lesions that are classified as positive remodeling because the lesion site EEM CSA is larger than the reference may, in reality, be lesions with exaggerated positive remodeling and exceptionally large plaque burdens. Lesions that are classified as negative remodeling because the lesion site EEM CSA is smaller than the reference may have undergone no change in arterial dimensions, but merely have less outward remodeling. This limitation to the standard IVUS methodology was highlighted in a recent review by Schoenhagen (6) prompting the current study. The fact that we saw significant negative remodeling in an important percentage of lesions with minimal reference segments disease supports the existence of arterial shrinkage as a real phenomenon that contributes to stenosis formation; 10% of group A lesions even had a remodeling index <0.80.

Classification of lesions as positive, intermediate, and negative remodeling is somewhat definition-dependent. Using one popular definition, we found that almost half of lesions associated with minimal reference segment disease can be classified as negative remodeling. Using another definition, we found that 34 of 91 (37%) group A lesions had an EEM CSA smaller than *both* the proximal and distal reference segments (vs. 22% of group B and 21% of group C lesions). Therefore, the current findings are not just a result of selecting a favorable definition.

Diabetes mellitus, hypercholesterolemia, gender, patient age, and multivessel disease were predictors of reference vessel segment plaque burden in one previous study (14). However, patient characteristics were similar among all three groups in the current analysis. These differences between the two studies might result from: 1) the extent of reference vessel segment plaque burden (28% in the current study vs. 51% in the previous study); 2) the younger age of the patients in the current study; 3) lesion location (right coronary artery alone vs. all three arteries); and 4) size of the study population (larger in the previous report). Ethnic differences and dietary habits might also contribute to these differences.

The dominant hypoechoic plaque characteristics, only small arcs of lesion calcium, larger angiographic and IVUS reference dimensions, and smaller reference plaque burden despite similar EEM CSA suggest that lesions in group A may be "younger" compared with group B and group C.

Study limitations. First, this was a retrospective study. Second, use of IVUS before coronary intervention depended on operator decision. Third, it is possible that reference segments with only minimal disease have already undergone positive remodeling. Fourth, we did not attempt to compensate for mechanical dilation if the IVUS catheter crossed a stenosis with a lumen smaller than the catheter. However, the impact of this mechanical dilation on lesion EEM would be modest (<0.75 mm^2, the CSA of the IVUS catheter), it would decrease the frequency of negative remodeling (by increasing lesion EEM), and would affect all three groups equally (pre-intervention lumen measurements were similar by angiography or IVUS). Fifth, volumetric IVUS analysis was not used in this study.

Conclusions. Negative remodeling occurs commonly in coronary lesions with minimal reference segment disease. Negative remodeling is not just an "artifact" introduced by comparing a lesion to diseased reference segments.

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